Atherosclerosis Plus 45 (2021) 32–38

Contents lists available at ScienceDirect

Atherosclerosis Plus

journal homepage: www.elsevier.com/locate/atherosclerosis

Effectiveness and safety of PCSK9 inhibitors in real-world clinical practice. An observational multicentre study. The IRIS-PCSK9I study

Marina Blanco-Ruiz [a, 1], Laura Amaya-Pascasio [a, 1], Reyes de Torres Chacón [b], María Josefa Álvarez Soria [c], Antonio Arjona-Padillo [a], María Magdalena Carrillo Bailén [c], Rodrigo Milán Pinilla [a], Irene Pérez Ortega [d], Belén Sánchez Rodríguez [e], Luis Andrade Zumárraga [a], Roberto Valverde Moyano [f], Manuel Payán Ortiz [a], Alba María Castillo Fernández [c], Cristina Del Toro Pérez [a], Pablo González Bustos [d], Eduardo Agüera Morales [f], Purificación Sánchez López [g], Beatriz Hidalgo Martín [c], Ricardo Roa Chamorro [d], Javier Fernández Pérez [a], María Victoria Mejías Olmedo [a], Patricia Martínez-Sánchez [a, *]

[a] Stroke Unit and Department of Neurology, Torrecárdenas University Hospital, Almería, Spain
[b] Stroke Unit and Department of Neurology, Virgen Macarena University Hospital, Seville, Spain
[c] Stroke Unit and Department of Neurology, Jaén University Hospital, Jaén, Spain
[d] Stroke Unit and Department of Neurology, Virgen de las Nieves University Hospital, Granada, Spain
[e] Department of Pharmacy. Torrecárdenas, University Hospital, Almería, Spain
[f] Stroke Unit and Department of Neurology, Reina Sofia University Hospital, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Spain
[g] Department of Internal Medicine, Torrecárdenas University Hospital, Almería, Spain

ARTICLE INFO

Article history:
Received 22 June 2021
Received in revised form
25 August 2021
Accepted 26 August 2021
Available online 3 October 2021

Keywords:
Evolocumab
Alirocumab
PCSK9i
Hypercholesterolemia familiar
Cardiovascular disease
Statins intolerance

ABSTRACT

Background and aims: The benefits of the PCSK9 inhibitors, alirocumab and evolocumab, in lowering LDL-cholesterol and preventing major adverse cardiac events (MACE) have been demonstrated in pivotal clinical trials. However, few studies of routine clinical practice have been conducted to analyse and compare the efficacy and safety of the two drugs.

Methods: Retrospective observational study of patients treated with a PCSK9 inhibitor in five hospitals in Andalusia (southern Spain). Baseline demographic and clinical data, LDL-cholesterol levels and the occurrence of MACEs during the follow-up period were recorded.

Results: A total of 141 patients were included in the study: 90 were treated with alirocumab and 51 with evolocumab. The patients' mean age (IQR) was 58 (11) years and 58 (41%) were women. The most frequent concomitant medications were statins, 94 (66.7%), followed by antiplatelet therapy (66%) and ezetimibe (65.2%). The median (IQR) follow-up period was 18 (18) months, with 18 (24) for alirocumab and 11 (18) for evolocumab. At the six-month follow-up visit, LDL-cholesterol values had decreased to pre-treatment levels and remained significantly decreased ($p < 0.05$) over time, for both drugs, and a greater reduction was achieved in patients with established cardiovascular disease and concomitant treatment with statins. With respect to adverse effects, there were nine MACEs (6.4%), of which seven were with alirocumab (7.8%) and two with evolocumab (3.9%) (p NS). Other adverse effects (9.2%) included local erythema (3.5%), muscle cramps (2.1%), respiratory symptoms (2.1%) and asthaenia (1.4%).

Conclusions: The efficacy and safety of alirocumab and evolocumab in routine clinical practice are consistent with the findings of the pivotal clinical trials.

Introduction

Reducing the level of low-density lipoproteins cholesterol (LDL-C) is one of the most important strategies employed to reduce the

* Corresponding author. Department of Neurology and Stroke Centre, Torrecárdenas University Hospital, University of Almería, Calle Hermandad de Donantes de Sangre S/N, 04009, Almería, Andalusia, Spain.
E-mail address: patrinda@ual.es (P. Martínez-Sánchez).
[1] Both authors contributed equally to the manuscript.

https://doi.org/10.1016/j.athplu.2021.08.009

risk of cardiovascular events, in both primary and secondary prevention [1,2]. Current European recommendations establish targets for LDL-C of <70 mg/dl or <55 mg/dl in patients with high or very high cardiovascular risk, respectively [3]. According to the ACC-AHA clinical practice guideline [1], in patients with atherosclerotic cardiovascular disease (CVD), LDL-C should be reduced with statins, either high-intensity or at the maximum tolerated dose. For patients at high or very high cardiovascular risk who do not meet the LDL-C goals despite treatment with full doses of statins, ezetimibe should be included in the usual therapy [1,3].

More than 80% of high-risk patients do not achieve the recommended LDL-C targets, mainly because of insufficient statins doses and patients' low adherence to chronic statin treatment, reaching less than 50% [4,5]. One of the main causes of non-adherence is intolerance to statins which can be defined as any adverse event (AEs) considered unacceptable by the patient, and/or the presence of laboratory abnormalities attributed to statin treatment and leading to its discontinuation or significant reduction to an insufficient dose [5,6]. The most frequently reported adverse effects are statin-associated muscle symptoms (10–29%), followed by laboratory abnormalities, headache, dyspepsia, nausea, alopecia and erectile dysfunction [5,6]. Furthermore, in some series up to 40% of patients are non-responders to statin therapy, defining non-responders as a decrease of less than 40% in LDL-C levels [7].

In view of these considerations, new therapies offering greater efficacy and safety are needed in order to increase adherence to treatment and enhance patients' satisfaction. Such a possibility is currently offered by proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i). Combinations of PCSK9i with statins and/or ezetimibe [8,9] may benefit patients who fail to achieve the expected therapeutic goals despite tolerable optimal treatment, as well as those who cannot tolerate standard medications.

Evolocumab and alirocumab are human IgG1 monoclonal antibodies which inhibit the PCSK9 serum protein [7,8]. PCSK 9 is a serine protease that regulates cholesterol metabolism through low-density lipoprotein receptor (LDLR) degradation before they reach the hepatic cell surface. As a result, the hepatic removal of LDL-C from the circulation decreases. When PCSK9 is blocked, more LDLR will reach the hepatic cell suface and, consequently, the uptake of circulating LDL-C will increase and LDL-C plasma levels will be lower [10,11]. Gain-of-function mutations in the PCSK9 gene are responsible for some forms of autosomal dominant hypercholesterolaemia [12].

Clinical trials have been conducted to evaluate the safety and effectiveness of PCSK9i in subjects with primary familial hypercholesterolaemia (FH) and in patients with CVD, compared to placebo or ezetimibe [8,9,13–20]. These studies have reported that both drugs showed significant reductions in LDL-C and significantly fewer major adverse cardiovascular events (MACEs) compared to placebo. In terms of the safety profile (i.e. rates of adverse events, AEs), no significant differences were observed between evolocumab, alirocumab and placebo, except for injection site reactions. Likewise, some research has been undertaken with respect to routine clinical practice, including different population with hypercholesterolemia. Most reported real-life experiences are consistent with the clinical trials [21–27].

Current guidelines recommend PCSK9i to treat established cardiovascular disease, FH and uncontrolled LDL-C, when statins do not produce a good response or in patients intolerant to statins in primary or secondary prevention [1,3].

The main objective of the present study was to confirm in a real world clinical settings the safety and efficacy of the use of PCKS9i in the management of hypercholesterolemia. As an exploratory analysis we analyse if there was any difference in the response to treatment according with the type of indication and between the two available monoclonal antibodies.

Patients and methods

Patient population and participating sites

This retrospective study was performed in the Neurology Departments of five tertiary referral hospitals in Andalusia (southern Spain) and included males and females over 18 years of age who were under treatment with alirocumab or evolocumab between January 2016 and November 2020. The funding criteria that were established by the Spanish Agency of Medicines and Medical Devices for PCSK9i treatment were: 1) uncontrolled FH (both drugs for heterozygosis but only evolocumab for homozygosis), defined as LDL-C greater than 100 mg/dl, with the maximum tolerated dose of statins; 2) patients with established CVD (ischaemic heart disease, ischaemic cerebrovascular disease and peripheral arterial disease) and uncontrolled LDL-C levels (defined as LDL-C greater than 100 mg/dl) under treatment with the maximum tolerated dose of statins; 3) any of the patients in the above groups who were intolerant to statins or in whom statins were contraindicated and had a LDL-C level greater than 100 mg/dl [28,29].

According to the characteristics of the included patients and their indication for the treatment with PCSK9i, we identified three main subgroups: FH patients under statin treatment and refractory hypercholesterolemia, subjects with established CVD and persistent elevated LDL-C levels despite statin use and statin-intolerant patients not meeting the LDL-C recommended targets. Refractory hypercholesterolemia was defined as an LDL-C level of 70 mg/dl or higher in high cardiovascular risk patients or a level of 100 mg/dl or higher without CVD [1,3,30].

Study design and data collection

An observational retrospective multicentre register was compiled, from standard clinical records, of patients under treatment with alirocumab or evolocumab. The collected clinical information was recorded in an anonymized electronic case report form that was managed by the neurologists of the Torrecardenas University Hospital as coordinating center. The study duration was 24 months.

The PCSK9i were dispensed from the hospital pharmacy every two months. The regular follow-up consisted of a hospital visit every 4–6 months and included the medical examination as well as blood tests. At the initial visit, demographic and baseline clinical data were obtained, including risk factors, previous illnesses, concomitant treatment and LDL-C. Arterial hypertension was defined as the need for antihypertensive medication, and hypertriglyceridaemia was defined as triglycerides >150 mg/dl. Subsequently, clinical and laboratory data, including LDL-C level, concomitant medication and any AE or MACE since the previous appointment were recorded in each follow-up visit. MACE was defined as myocardial infarction, ischaemic stroke, death from ischaemic heart disease and hospitalisation for unstable angina [8,9].

Ethics

The study protocol is in accordance with the ethical guidelines

of the 1975 Declaration of Helsinki, including all subsequent amendments. The project was approved by the Clinical Research Ethics Committee of the Torrecárdenas University Hospital and obtained authorisation from the Spanish Agency of Medicines. The data collected for the study were processed in accordance with the General Data Protection Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016. Due to the retrospective nature of the study, an exemption from signing the informed consent was approved by the local Ethics Committee.

Data analysis

The statistical analysis was performed using IBM SPSS Statistics for Mac, Version 25.0, software (IBM Corp. Armonk, NY, USA) and R statistics for Mac. For the quantitative variables, the mean and standard deviation, the median and the interquartile range were calculated. The qualitative data are described using absolute and relative frequencies. Comparisons between the two treatment groups were carried out using parametric or non-parametric tests. When the samples presented homoscedasticity and normal distribution, the T-test was used to compare the quantitative variables, otherwise the Mann-Whitney test was applied. In the comparisons of adverse effects, in all cases, the normality test used was the Anderson-Darling test. Homoscedasticity was evaluated by the Fligner-Killeen test.

The evolution of LDL-C over time was analysed by comparison tests of the means for repeated measures. In this process, we first determined whether the ANOVA residuals were normal, according to the Shapiro test, and homoscedastic. Since the above conditions were not met, the differences were evaluated with an ANOVA equivalent non-parametric measure, the Friedman test, together with a post-hoc Durbin-Conover test to perform a pairwise comparison between the months. The p-values of these post-hoc tests were adjusted by Holm's method. The differences of the mean LDL-C reduction between the three subgroups according to the indication for PCSK9i treatment were stimated with the Kruskal-Wallis test.

A MACE-free survival exploratory analysis was performed using the Kaplan-Meier estimator, for each of the treatment groups: evolocumab and alirocumab.

A p-value < 0.05 was considerer statiscally significant in all tests.

Results

The main baseline characteristics are shown in Table 1. A total of 141 patients were included in the study group, of whom 90 were treated with alirocumab and 51 with evolocumab. The median age of all the included patients was 58 (IQR 11). The median age of those treated with alirocumab or evolocumab were 59.3 (IQR 9.5) and 60.0 (IQR 7.6), respectively (p NS). Fifty-eight of the patients (41%) were women. Of these, 41 (45.6%) received alirocumab and 17 (33.3%), evolocumab (p NS).

Among the vascular risk factors considered, arterial hypertension was the most prevalent in the sample group (59.6%), closely followed by tobacco use (57.4%). Ischaemic heart disease, present in 58.9% of the sample, was the most prevalent CVD.

Regarding indications for treatment, 44% of the patients had CVD and refractory hypercholesterolaemia despite receiving statin treatment. In 42.6% of patients, the PCSK9i was employed, due to statin intolerance, and 13.5% presented FH (16.7% of the patients treated with alirocumab and 7.8% of those treated with evolocumab). The most frequent concomitant medications were statins, for 94 (66.7%) of the total group, for 56 (62.2%) of those treated with alirocumab and 38 (74.5%) of those treated with evolocumab, followed by antiplatelet therapy (66%) and ezetimibe (65.2%). A total of 25 (17.7%) patients were under treatment with oral antidiabetic agents, of those 6 (24%) were benefiting from a SGLT2 inhibitor. No patient was treated with a GLP1 antagonist. Likewise, among the patients classified as statin-intolerant, 15 subjects (25%) were on a low-dose statin treatment, mainly rosuvastatin 10 mg and atorvastatin 10 mg. All the patients included in the FH and the established CVD subgroups were under high-dose statin treatment.

The median follow-up period was 18 (IQR 18) months, 18 (IQR 24) months for alirocumab and 11 (IQR 18) months for evolocumab. LDL-C values decreased between the pre-treatment evaluation and the six-month follow-up visit and remained significantly decreased ($p < 0.05$) over time (at the 12, 18, 24 and 30-month follow-ups), as shown in Fig. 1. The mean percentage of LDL-C reduction from baseline to the six-month follow-up were 50% (SD 47), 46.6% (SD 29) for alirocumab and 48% (SD 70) for evolocumab. The mean absolute LDL-C reduction was 84 mg/dl (SD 57): 79 mg/dl (SD 57) for alirocumab and 92 mg/dl (SD 57) for evolocumab. There was a greater global mean absolute reduction of LDL-C in the non-controlled CVD group compared to the FH and statin-intolerance groups: 95 mg/dl (SD 49), 88 mg/dl (SD 63) and 71 mg/dl (SD 61), respectively ($p < 0.001$), which corresponds to a reduction percentage of 64%, 45% and 32%. Regarding the presence of concomitant treatment, the patients treated with statins achieved a 52% (SD 51) LDL-C mean reduction at six months, in contrast to the 39% (SD 36) LDL-C mean reduction (p 0.002) achieved by those who did not receive this treatment (Fig. 2). A total of 87 patients (69,6%) achieved LDL-C levels <100 mg/dl in the first follow-up visit.

Only two new types of MACE were notified during the follow-up period: hospitalisation for unstable angina and myocardial infarction. These conditions affected 6.4% of all patients (7.8% of the alirocumab group and 3.9% of the patients treated with evolocumab), as shown in Table 2. Up to 89% of patients who presented a MACE had history of ischemic heart disease and, in one case, the patient had previously suffered an ischemic stroke. The exploratory analysis (Fig. 3) showed that there were no significant differences between the two PCSK9i regarding the rate of MACE and the MACE-free periods.

A comulative AEs rate of 9.2% was recorded at the end of the study, 69.2% of cases were reported at the first visit (6 months) and 30.7% at the 12-month visit, remaining the 23% persistent during the follow-up. The most frequent was injection-site reaction (3.5%), followed by muscle cramps (2.1%), respiratory symptoms (2.1%) and asthaenia (1.4%). In this respect, there were no significant differences between the two medications (Table 2). Most of the AEs were mild and did not lead to drug discontinuation.

Discussion

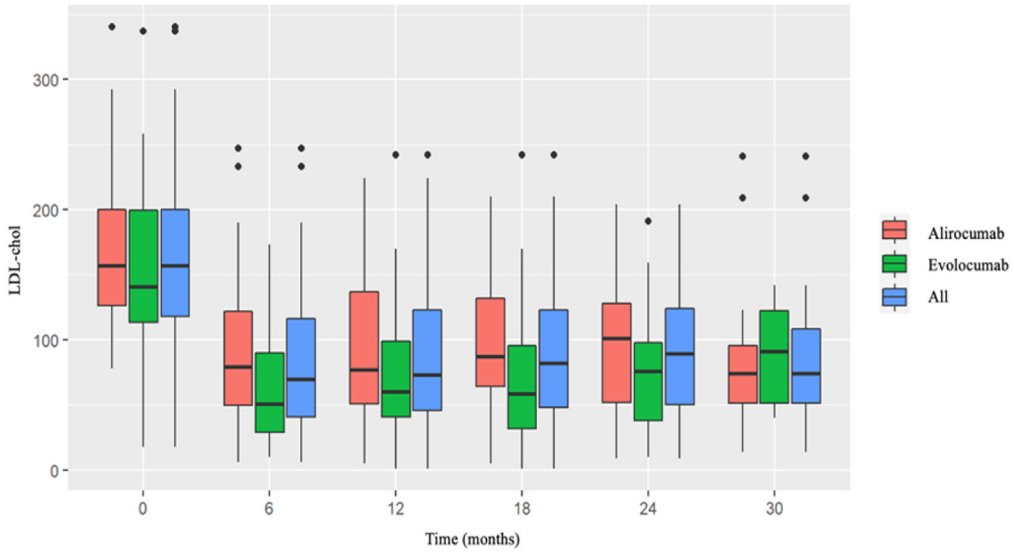
This real-world study analyses the efficacy and tolerance of PCSK9i among a population of Spanish patients comparing three subgroups of patients with different hypercholesterolaemia profiles. As an exploratory analysis, the clinical data obtained for alirocumab and evolocumab were also compared. Our results are similar to those obtained in the pivotal trials, both drugs showed a similar efficacy and safety profile and a greater reduction in the LDL-C levels was achieved in the subgroup of patients with established CVD and concomitant treatment with statins.

The sociodemographic characteristics of our target population, regarding age and sex, are comparable to those described in

Table 1
Baseline characteristics.

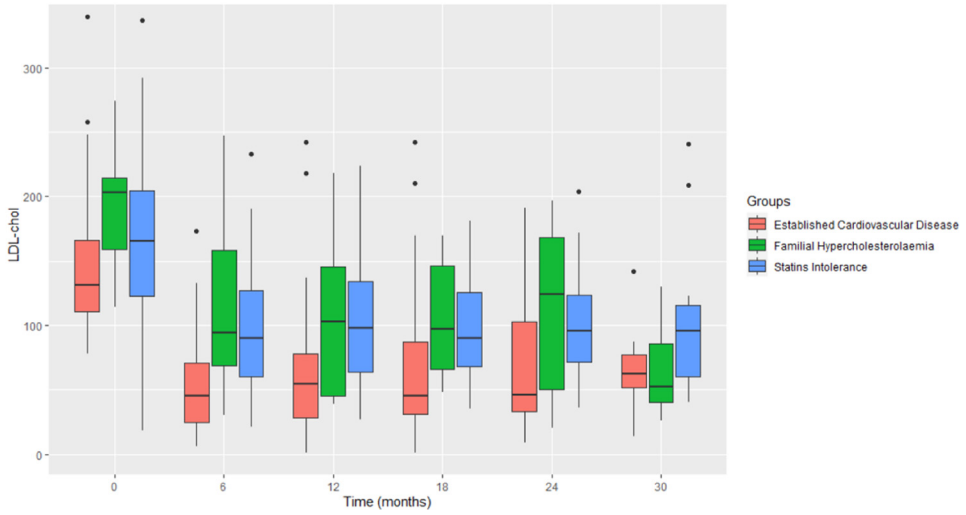
	All (N = 141)	Alirocumab (N = 90)	Evolocumab (N = 51)	P[a]
Demographic data				
Age (IQR), years	58 (11)	59.3 (9.5)	60.0 (7.6)	0.395
Weight (IQR), kg	79.2 (21.6)	76.0 (22.9)	80.0 (21.2)	0.268
Female gender, n (%)	58 (41.0%)	41 (45.6%)	17 (33.3%)	0.156
Vascular risk factors and comorbidities				
Arterial hypertension, n (%)	84 (59.6%)	53 (58.9%)	31 (60.8%)	0.826
Smoker/former smoker, n (%)	81 (57.4%)	49 (54.4%)	32 (62.7%)	0.338
Diabetes, n (%)	32 (22.7%)	17 (18.9%)	15 (29.4%)	0.152
Hypertriglyceridaemia, n (%)	52 (36.9%)	31 (34.4%)	21 (41.2%)	0.426
Familial hypercholesterolaemia, n (%)	19 (13.5%)	15 (16.7%)	4 (7.8%)	0.140
Ischaemic heart disease, n (%)	83 (58.9%)	53 (58.9%)	30 (58.8%)	0.994
Atrial fibrillation, n (%)	6 (4.3%)	3 (3.3%)	3 (5.9%)	0.471
Chronic arterial ischaemia, n (%)	13 (9.2%)	5 (5.6%)	8 (15.7%)	0.046
Previous myocardial infarction, n (%)	2 (1.4%)	0 (0%)	2 (3.9%)	0.058
Previous stroke, n (%)	13 (9.2%)	8 (8.9%)	5 (9.8%)	0.857
Chronic kidney disease[b], n (%)	15 (10.6%)	7 (5.0%)	8 (5.7%)	0.143
Concomitant treatment				
Statins, n (%)	94 (66.7%)	56 (62.2%)	38 (74.5%)	0.137
Ezetimibe, n (%)	92 (65.2%)	58 (64.4%)	34 (66.7%)	0.790
Oral antidiabetic, n (%)	25 (17.7%)	15 (16.6%)	10 (19.6%)	0.356
Antiaggregant, n (%)	93 (66.0%)	55 (39.0%)	38 (27.0%)	0.107
ACE inhibitors, n (%)	53 (37.6%)	34 (37.8%)	19 (37.3%)	0.951
Angiotensin II receptor blockers, n (%)	33 (23.4%)	20 (22.2%)	13 (25.5%)	0.660
Beta-blockers, n (%)	67 (47.5%)	38 (42.2%)	29 (56.4%)	0.094
Calcium channel blockers, n (%)	26 (18.4%)	14 (15.6%)	12 (23.5%)	0.241
Alpha-blockers, n (%)	11 (7.8%)	4 (4.4%)	7 (13.7%)	0.048
Diuretics, n (%)	37 (26.2%)	24 (26.7%)	13 (25.5%)	0.879
Anticoagulants, n (%)	13 (9.2%)	6 (6.7%)	7 (13.7%)	0.164
Insulin, n (%)	11 (7.8%)	4 (4.4%)	7 (13.7%)	0.048

[a] The value of p is the result of comparing the values of alirocumab vs. evolocumab. IQR, interquartile range.
[b] The severity of chronic kidney disease was variable, including all stages of the disease.



Patients (n)	0	6	12	18	24	30
All	140	121	81	65	58	30
Alirocumab	90	80	57	45	41	22
Evolocumab	51	41	24	20	17	8

Fig. 1. Graphic representation of the variation in LDL-cholesterol levels during follow-up visits.
In all cases, the non-parametric Friedman test is used, as there was no normality in LDL levels in the time periods when the measurements were taken. This test was calculated for the first 18 months follow-up period with n = 56. According to this test, the LDL levels, for the two drugs separately and overall, fell significantly ($p < 0.05$) between month 0 (baseline) and the six-month follow-up, but then stabilised.
The table shows the number of patients (n) and the LDL-cholesterol levels recorded for each time period.



Patients (n)	0	6	12	18	24	30
Established CVD	62	51	32	21	17	8
FH	19	17	14	13	13	8
Statins Intolerance	60	53	35	31	28	14

Fig. 2. Graphic representation of the variation in LDL-cholesterol levels during follow-up visits by subgroups.
In all cases, the non-parametric Friedman test is used, as there was no normality in LDL levels in the time periods when the measurements were taken. This test was calculated for the first 18 months follow-up perido
with n = 56. According to this test, the LDL levels, for the three subgroups according to the indication for PCSK9i treatment fell significantly ($p < 0.05$) between month 0 (baseline) and the six-month follow-up, but then stabilised.
The table shows the number of patients (n) and the LDL-cholesterol levels recorded for each time period.
CVD: Cardiovascular disease. FH: Familial hypercholesterolaemia.

Table 2
Description of the number of MACE and adverse events and the time until they were notified.

	All (N = 141)	Alirocumab (N = 90)	Evolocumab (N = 51)	*P*
MACE, n (%)	9 (6.4%)	7 (7.8%)	2 (3.9%)	0.368
Hospitalisation for unstable angina, n (%)	7 (5.0%)	5 (5.6%)	2 (3.9%)	0.668
Myocardial infarction, n (%)	2 (1.4%)	2 (2.2%)	0 (0.0%)	0.284
Death for ischaemic heart disease	0 (0%)	0 (0%)	0 (0%)	–
Ischaemic stroke	0 (0%)	0 (0%)	0 (0%)	–
Time to MACE (months), median (IQR)	12 (6–18)	12 (6–18)	9 (6–9)	0.503
Advers events, n (%)	13 (9.2%)	10 (11.1%)	3 (5.9%)	0.302
Reaction in the injection side, n (%)	5 (3.5%)	4 (4.4%)	1 (2.0%)	0.444
Muscle cramps, n (%)	3 (2.1%)	3 (3.3%)	0 (0.0%)	0.188
Respiratory symptoms, n (%)	3 (2.1%)	1 (1.1%)	2 (3.9%)	0.266
Asthaenia, n (%)	2 (1.4%)	2 (2.2%)	0 (0.0%)	0.284
Time to AE (months), median (IQR)	6 (6–12)	6 (6–9)	9 (6–12)	0.500

MACE, major adverse cardiovascular events: death from ischaemic heart disease, myocardial infarction, ischaemic stroke, and hospitalisation for unstable angina. IQR: Interquartile range. AE: Advers events.
a The p value is obtained from comparing the values of alirocumab vs. evolocumab.

previous clinical trials [8,9,13–20]. In our sample, hypertension was the most prevalent risk factor and, as in the trials that included patients with CVD, ischaemic heart disease was the main cardiovascular comorbidity. However, when the concomitant treatment was taken into account, the patients in our study groups presented a lower percentage of medication with statins than has been reported in most previous studies [8,9,17,20].

Among our cohort, the main reason for treatment with PCSK9i was refractory hypercholesterolaemia despite the provision of standard treatment for patients with established CVD. This factor was followed by statin intolerance, with FH being the third most common indication. Similar PCSK9i treatment indications have been reported in other real-world studies analysing the use of these drugs, although in most cases the percentage of patients with FH was higher [31–33]. The rate of statin intolerance in our sample was higher than that reported by Rane et al. (31.6%), in a real-world study carried out in the USA, but lower than that reported by Zafrir et al. (77%) [32]. In the latter study, only 40.5% of the patients being treated with alirocumab or evolocumab had concomitant treatment with statins, versus the 66.7% reported in our population.

The PCSK9i clinical trials [8,9,13–20] reported an LDL-C reduction of around 50% from the baseline values, which was significantly greater than in the placebo and ezetimibe groups. In the same line, Zafrir et al. analysed 101 patients treated with PCSK9i and reported a mean LDL-C reduction of 59%. These authors observed that the LDL-C reduction achieved by the patients with heterozygous FH was similar to that of the non-FH patients [32]. These results are consistent with the mean overall LDL-C reduction in our series. However, we observed that among the patients with FH, the LDL-C decreased less than in the other groups, possibly due

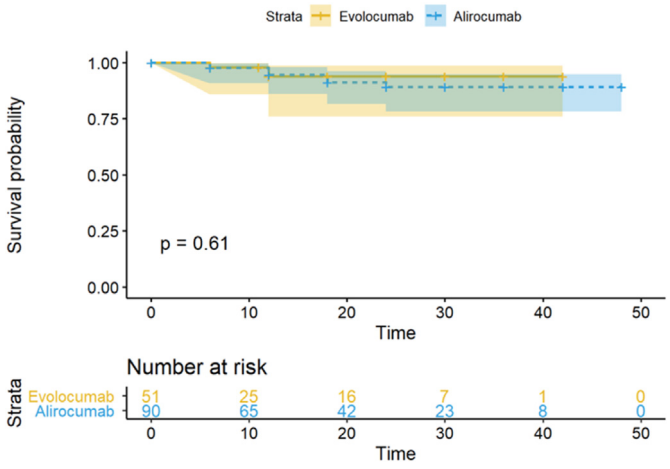


Fig. 3. MACE-free survival throughout the study
[a] Since the log-rank test is not significant ($p > 0.05$), there are no statistically significant differences between the MACE-free survival curves for the two treatments.

to the different molecular mechanisms and/or the clinical heterogeneity underlying this disease [34]. Nevertheless, the reduction was greater among the patients with no FH but who presented CVD. It was also greater for the patients receiving concomitant treatment with statins, which corroborates Hollstein at al., according to whom there was a 7.1% greater mean LDL-C reduction in patients receiving statins than in those not receiving them because of intolerance. The overall pattern of LDL-C levels reported by these authors was similar to that observed in our study, with a stronger decrease during the first four weeks of treatment, followed by stable LDL-C values during the follow-up period [27]. Randomized clinical trials and real-world studies with a longer follow-up period confirmed that the effects of PCSK9i were maintained over time for most patients [13,19,27,35].

Recently, a Spanish group has published a multicentre, real-life study including 154 patients with hypercholesterolaemia treated with PCSK9i and a follow-up period between 3 and 24 months [36]. Compared to our study, the treatment with Evolocumab was more frequent (58% vs 36%), and there was a higher percentage of patients with FH (29.9% *vs.* 13,5%). The global LDL-C reduction was similar; however, the MACE rate was slightly lower than in our cohort (3.9% *vs.* 6.4%), possibly due to differences in the follow-up period and the small sample size. The ODYSSEY LONG TERM study [13] monitored patients treated with alirocumab for up to 78 weeks, and recorded a MACE rate of 6.3%, significantly lower than in the placebo group. Regarding evolocumab, the FOURIER study [8] observed a MACE rate of 9.8%, with a median follow-up of 26 months. In our study, only two types of MACE were detected, myocardial infarction and hospitalisation for unstable angina. In both cases, the frequencies observed were similar to those reported previously.

Both evolocumab and alirocumab were generally well tolerated. Only minor side effects were noticed, and no major AE was notified. This is consistent with previous clinical trials [8,9,13–20], which only reported a significantly higher injection-site reaction rate in the PCSK9i group compared to the placebo group. Hollstein et al. [27], whose study group included 635 patients, reported an overall rate of minor adverse events of 47.1%, with rhinitis, fatigue and myalgia being the most common. After 68 weeks, 8.7% of these patients had discontinued PCSK9i treatment because of AEs.

This study examined the use of PCSK9i in clinical practice and observed no significant differences in the reduction of LDL-C, the incidence of MACEs or the presence of AEs. However, the included sample and the mean follow-up period were small and so was the rate of MACE, which limits the generalisability of our findings.

Conclusion

In terms of drug efficacy and safety, the results of the present study are similar to those obtained in the pivotal trials of alirocumab and evolocumab. With respect to the reductions in LDL-C and in the incidence of MACEs and AEs, the two drugs were comparable. The results of this real-world study support the use of PCSK9i in patients who do not achieve optimal cholesterol control.

Financial support

No institutional financing was received for this study.

Author contributions

All authors, except L. A-M., were involved in the development of the IRIS-PCSK9 protocol. All took part in the evaluation and interpretation of the study results and have reviewed and approved the final manuscript. M. B-R, L. A-M and P. M-S. prepared the manuscript, in coordination with all other co-authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Our thanks to FIBAO and to the BIOSTATECH company for assisting with the statistical analysis of our results.

References

[1] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith Jr SC, Virani SS, Williams Sr KA, Yeboah J, Ziaeian B. ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Circulation 2019;140(11):e596–646. https://doi.org/10.1161/CIR.0000000000000678. Epub 2019 Mar 17. Erratum in: Circulation. 2019 Sep 10;140(11):e649-e650. Erratum in: Circulation. 2020 Jan 28;141(4):e60. Erratum in: Circulation. 2020 Apr 21;141(16):e774. PMID: 30879355; PMCID: PMC7734661, 2019 Sep. 10.

[2] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387–97.

[3] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, ESC Scientific Document Group. ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J 2019;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455. Erratum in: Eur Heart J. 2020 Nov 21;41(44):4255. PMID: 31504418, 2020 Jan 1.

[4] Gislason GH, Rasmussen JN, Abildstrom SZ, Gadsboll N, Buch P, Friberg J, Rasmussen S, Kober L, Stender S, Madsen M, Torp-Pedersen C. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. Eur Heart J 2006;27:1153–8. https://doi.org/10.1093/EURHEARTJ/EHI705.

[5] Alonso R, Cuevas A, Cafferata A. Diagnosis and management of statin intolerance. J Atherosclerosis Thromb 2019 Mar 1;26(3):207–15. https://doi.org/10.5551/jat.RV17030. Epub 2019 Jan 19. PMID: 30662020; PMCID: PMC6402887.

[6] Brown AS, Watson KE. Statin intolerance. Rev Cardiovasc Med 2018;19(S1):S9–19.

[7] Trompet S, Postmus I, Slagboom PE, Heijmans BT, Smit RA, Maier AB, Buckley BM, Sattar N, Stott DJ, Ford I, Westendorp RG, de Craen AJ, Jukema JW. Non-response to (statin) therapy: the importance of distinguishing non-responders from non-adherers in pharmacogenetic studies. Eur J Clin

Pharmacol 2016 Apr;72(4):431–7.
[8] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22. https://doi.org/10.1056/NEJMOA1615664.
[9] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–107.
[10] Horton JD, Cohem JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J Lipid Res 2009;50:Suppl. https://doi.org/10.1194/JLR.R800091-JLR200.
[11] Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. Nat Rev Cardiol 2018;163(16):155–65. https://doi.org/10.1038/s41569-018-0107-8. 2018.
[12] Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154–6. https://doi.org/10.1038/NG1161.
[13] Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, et al. ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372(16):1489–99. https://doi.org/10.1056/NEJMOA1501031.
[14] Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, Kim JB, Scott R, Wasserman SM, Bays H, MENDEL-2 Investigators. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2531–40. https://doi.org/10.1016/J.JACC.2014.03.018.
[15] Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, Somaratne R, Legg JC, Nelson P, Scott R, Wasserman SM, Weiss R. LAPLACE-2 Investigators, Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. J Am Med Assoc 2014;311:1870–82. https://doi.org/10.1001/JAMA.2014.4030.
[16] Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, Bruckert E, Cho L, Dent R, Knusel B, Xue A, Scott R, Wasserman SM, Rocco M. GAUSS-2 Investigators, Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2541–8. https://doi.org/10.1016/J.JACC.2014.03.019.
[17] Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, Langslet G, Scott R, Olsson AG, Sullivan D, Hovingh GK, Cariou B, Gouni-Berthold I, Somaratne R, Bridges I, Scott R, Wasserman SM, Gaudet D, RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2015;385:331–40. https://doi.org/10.1016/S0140-6736(14)61399-4.
[18] Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, Ceska R, Roth E, Koren MJ, Ballantyne CM, Monsalvo ML, Tsirtsonis K, Kim JB, Scott R, Wasserman SM, Stein EA, Descartes Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014;370:1809–19. https://doi.org/10.1056/NEJMOA1316222.
[19] Raal FJ, Hovingh GK, Blom D, Santos RD, Harada-Shiba M, Bruckert E, Couture P, Soran H, Watts GF, Kurtz C, Honarpour N, Tang L, Kasichayanula S, Wasserman SM, Stein EA. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. Lancet. Diabetes Endocrinol. 2017;5:280–90. https://doi.org/10.1016/S2213-8587(17)30044-X.
[20] Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA. TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2015;385:341–50. https://doi.org/10.1016/S0140-6736(14)61374-X.
[21] Reynolds T, Carey P, George J, Konidaris G, Narayanan D, Ramachandran S, Saunders L, Viljoen A, Ferns G. A retrospective observational study to determine baseline characteristics and early prescribing patterns for patients receiving alirocumab in UK clinical practice. Drugs - Real World Outcomes 2019;64(6):205–13. https://doi.org/10.1007/S40801-019-00166-7. 2019.
[22] Sarsam S, Berry A, Degheim G, Singh R, Zughaib M. Real-world use of PCSK9 inhibitors: A single-center experience. 47, https://doi.org/10.1177/0300060518800595; 2018. 265-270.
[23] Ceballos-Macías JJ, Lara-Sánchez C, Flores-Real J, Aguilar-Salinas CA, Ortega-Gutiérrez G, et al. PCSK-9 inhibitors in a real-World setting and a comparison between alirocumab and evolocumab in heterozygous FH patients. J. Endocr. Soc. 2021;5:1–6. https://doi.org/10.1210/JENDSO/BVAA180.
[24] Yokote K, Ako J, Kitagawa K, Inomata H, Sugioka T, et al. 12-Week effectiveness and safety of low-density lipoprotein cholesterol-lowering therapy by proprotein convertase subtilisin/Kexin type 9 inhibition in patients With familial hypercholesterolemia and hypercholesterolemia - data from a real-World observational study of evolocumab in Japan. Circ. Reports 2019;1:219–27. https://doi.org/10.1253/CIRCREP.CR-19-0027.
[25] Saborowski M, Dölle M, Manns MP, Leitolf H, Zender S. Lipid-lowering therapy with pcsk9-inhibitors in the management of cardiovascular high-risk patients: effectiveness, therapy adherence and safety in a real world cohort. Cardiol J 2018;25:32–41. https://doi.org/10.5603/CJ.A2017.0137.
[26] Tai M-H, Shepherd J, Bailey H, Williams N, Hatz M, Tapias IC, Catterick D, Worth G. Real-world treatment patterns of PCSK9 inhibitors among patients with dyslipidemia in Germany, Spain, and the United Kingdom. 2018. p. 829–35. https://doi.org/10.1080/03007995.2018.1532885. Https://Doi.Org/10.1080/03007995.2018.1532885. 35.
[27] Hollstein T, Kassner U, Grenkowitz T, Schumann F, Bobbert T, Steinhagen-Thiessen E. PCSK9 inhibitors in a German single-center clinical practice: real-World treatment of patients at high cardiovascular risk over 68 weeks. Am J Cardiovasc Drugs 2020;211(21):83–92. https://doi.org/10.1007/S40256-020-00411-3. 2020.
[28] Informe de Posicionamiento Terapéutico de Evolocumab (Repatha ®) En hipercolesterolemia, (n.d.).
[29] Informe de Posicionamiento Terapéutico de Alirocumab (Praluent®). en hipercolesterolemia - Agencia Española de Medicamentos y Productos Sanitarios (n.d.), https://www.aemps.gob.es/informa/informes-de-posicionamiento-terapeutico/informe-de-posicionamiento-terapeutico-de-alirocumab-praluent-en-hipercolesterolemia/. accessed July 22, 2021.
[30] Rosenson RS, Burgess LJ, Ebenbichler CF, Baum SJ, et al. Evinacumab in patients with refractory hypercholesterolemia. 2020. p. 2307–19. https://doi.org/10.1056/NEJMOA2031049. Https://Doi.Org/10.1056/NEJMoa2031049. 383.
[31] Piccinni C, Antonazzo IC, Maggioni AP, Pedrini A, Calabria S, Ronconi G, Dondi L, Martini N, Roberto G, Sampietro T, Sbrana F, Pino BD, Bigazzi F, Surdo GL, Volpi E, Biagini S, Gini R. PCSK9 Inhibitors' new users: analysis of prescription patterns and patients' characteristics from an Italian real-world study. Clin Drug Invest 2020 Feb;40(2):173–81. https://doi.org/10.1007/s40261-019-00877-3. PMID: 31797311.
[32] Zafrir B, Jubran A. Lipid-lowering therapy with PCSK9-inhibitors in the real-world setting: two-year experience of a regional lipid clinic. Cardiovasc Ther 2018 Oct;36(5):e12439. https://doi.org/10.1111/1755-5922.12439. Epub 2018 Jun 28. PMID: 29863817.
[33] Rane PB, Patel J, Harrison DJ, Shepherd J, Leith A, Bailey H, Piercy J. Patient characteristics and real-world treatment patterns among early users of PCSK9 inhibitors. Am J Cardiovasc Drugs 2018 Apr;18(2):103–8. https://doi.org/10.1007/s40256-017-0246-z. PMID: 28849360.
[34] Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, Watts GF, Baum SJ, Catapano AL, Chapman MJ, Defesche JC, Folco E, Freiberger T, Genest J, Hovingh GK, Harada-Shiba M, Humphries SE, Jackson AS, Mata P, Moriarty PM, Raal FJ, Al-Rasadi K, Ray KK, Reiner Z, Sijbrands EJ, Yamashita S. International Atherosclerosis society severe familial hypercholesterolemia panel. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the international Atherosclerosis society severe familial hypercholesterolemia panel. Lancet Diabetes Endocrinol 2016 Oct;4(10):850–61. https://doi.org/10.1016/S2213-8587(16)30041-9. Epub 2016 May 27. Erratum in: Lancet Diabetes Endocrinol. 2016 Aug;4(8):e8. PMID: 27246162.
[35] D'Erasmo L, Commodari D, Di Costanzo A, Minicocci I, Polito L, Ceci F, Montali A, Maranghi M, Arca M. Evolving trend in the management of heterozygous familial hypercholesterolemia in Italy: a retrospective, single center, observational study. Nutr Metabol Cardiovasc Dis 2020;30:2027–35. https://doi.org/10.1016/J.NUMECD.2020.06.028.
[36] Gayoso-Rey M, Díaz-Trastoy O, Romero-Ventosa EY, García-Beloso N, González-Freire L, Lorenzo-Lorenzo K, Mantiñán-Gil B, Palmeiro-Carballeira R, Bravo-Amaro M, López-Gil-Otero MDM, Martínez-Reglero C, Crespo-Diz C, Fernández-Catalina P, Piñeiro Corrales G. Effectiveness, safety, and adherence to treatment of proprotein convertase subtilisin/Kexin type 9 inhibitors in real practice. Clin Therapeut 2021 Apr;43(4):e111–21. https://doi.org/10.1016/j.clinthera.2021.02.002. Epub 2021 Mar 9. PMID: 33712271.